ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

BREAKOUT GROUP DISCUSSION - MONOGASTRICS

WEDNESDAY, FEBRUARY 23, 2000

2:00 P.M.

DOUBLETREE INN

1750 Rockville Pike

Rockville, Maryland

Gazebo

I N D E X

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Keynote: "---" indicates an inaudible in the transcript.

BREAKOUT GROUP DISCUSSION - MONOGASTRICS

(2:15 p.m.)

CO-CHAIRPERSON SINDELAR: Hi; thanks for coming out here to the gazebo. I'm sorry for the time delay that we have incurred. I don't think most of us could have endured the conditions in the Twinbrook Room and it is likely that we will meet here again tomorrow morning. I doubt that they will have the room totally aired by then.

I just want to go over some of the changes that we've made as a result of making this switch out of the Twinbrook Room and so -- and these include -- because we have this time shortened, we would like to have a working break.

Now, that break is from 3:00 until 3:30. I apologize if you have any, you know, communications you must make but would you -- could we please continue through this afternoon in discussing these issues.

This is a working group to collect input. It is not a consensus gathering exercise. We are looking for content. We have, as you know, Dr. Morrison and Chuck Andres. So if you have any questions, you know, after the meeting you can approach any of us regarding the context that we have discussed here in the meeting.

As I said, these -- Chuck will be gathering the more salient points that we address in response to each of the five questions. In addition, we'll be addressing the issues that

came up this morning and all comments will be transcribed so it is very important that you use the microphone in order for us to accurately record all of the information exchanged. And with that, I'll give you to Dr. Morrison.

INTRODUCTION

CHAIRMAN MORRISON: I'm just wondering, Aleta, if you want me to -- I mean, to have -- sort of have a dialogue exchange. People are probably going to be fairly comfortable sitting where they are, if I or one of us should just carry the microphone around or pass it around or if you'd prefer to come up to the front. Do you have a preference? If you don't have a preference, we'll leave the microphone there.

VOICE: Leave it there.

CHAIRMAN MORRISON: Leave it there? Okay. Bill Flynn came out and suggested to us that we start with the question that was raised this morning that is not one of the five that is on your sheets and that is the one that Chuck has put up there, that being, what do you think should be or are the objectives of the pre-approval studies?

DISCUSSION/QUESTION/ANSWER

DR. BROWN: Scott Brown, Pharmacia & Upjohn. I think one of the things we have to keep in mind is that by the implication of the use of the term pre-approval studies, there is an implication that something happens with respect to approval as a result of these studies, and I think we need to

be -- I think this is something we actually need to come to consensus on before we actually define what we're going to be doing.

We can get a lot of brainstorming in on what kinds of studies and what aspects of things, but unless we know what are end is in mind, there's going to be a lot of things that are really going to be kind of useless discussions.

My suggestion, to start off with anyway, is to have these pre-approval studies that are designed to modulate what categories a product might be put into. And obviously, as a discussion, some things have already been discussed by FDA.

There is a process in place through the Framework document to put things in compounds and categories. It seems to me like these pre-approval studies might be useful to actually modulate what category a compound might be in which then in turn will drive what sorts of post-approval monitoring and mitigating factors -- or mitigating actions are taken as a result.

As an example, something that might be in a category one to begin with, if there were some pre-approval studies that showed that there was a substantially lower mutation frequency than the rest of the compounds in the same class of compounds, then that might be a reason to argue that it would not be a category one compound but rather a category two because of that

difference in the mutation frequency that might be seen.

So that's an example I think we ought to be keeping in mind and have some agreement about what these studies are intended to do, pre-approval. If they aren't making decisions about the approval, then they are essentially done regardless of what the approval is.

Whether it's pre-approval or post-approval, it makes no difference. If it's pre-approval, then by implication, there is a decision about the approval that is made upon these studies.

CHAIRMAN MORRISON: Let me make sure I understand one thing, Chuck. When a proposed drug comes in for a pre-approval study, or a series of studies, is it already categorized? Is that the idea? Or is what Scott said, what I understood, that the pre-approval studies will provide information to help with the categorization of the drug?

MR. ANDRES: Well, I think that --

CHAIRMAN MORRISON: Here, hang on.

MR. ANDRES: Hand me the microphone. I could probably answer that question by saying yes to both of them and not being facetious. I think as we work through how we're going to implement the Framework document and whether something is a category one or two, we're looking -- that's one of the reasons why we're here, is to get input as to how best we implement this document.

So when we start talking about you bringing a compound in, let's say would be normally classified as a category one; however, it has a reduced frequency in mutation, could we maybe say, well, different types of studies could probably be used to address our concern than what would traditionally be required for a category one product.

Certainly the fact that we've stuck the pre-approval -- you've hit it on the head. Is that -- the approval is going to be contingent upon what the outcome of those studies are.

So without getting into anything other than that, that's probably a good place to start, that if you assume they're pre-approval studies, they're not post-approval, they have to be completed in some type of --- resolution or decision is going to be made on the basis of the outcome of those studies.

CHAIRMAN MORRISON: So that, then, is a reasonable objective for the pre-approval studies.

MR. ANDRES: Yes.

CHAIRMAN MORRISON: To provide information on the categorization of the drug.

DR. McEWEN: Scott McEwen from the University of Guelph. I guess, in addition to categorization of the drug with respect to the human health importance, I think that the pre-approval study should contain information that would be

useful for a categorization of the extent of exposure, which I understand from the Framework document, there's the two types of categorization and presumably drugs would be then placed within a grid.

And I think, given what we heard yesterday and some of the discussion from Fred this morning, that much of the information would pertain to the latter categorization, that is, the extent of exposure, both in terms of frequency of mutation, the frequent prevalence of resistance, and also I think in terms of the types of applications the drug is going to be used for.

That was implicit, I think, in Fred's comment about the feed use. But, in a broader sense, it should be all those things that pertain to potential exposure.

CHAIRMAN MORRISON: And so, both of those points, the little bit I understand about the Framework -- correct me if I'm wrong, but both of those points would then become -- would go into the categorization of the drug, that degree of exposure and its use or its other uses. Is that right?

DR. McEWEN: Yes. Scott McEwen again. I don't have a copy of the Framework document here. If somebody does, we could maybe get it and search for the wording, but I think we should maybe seek that out and find out what the proper wording is with respect to -- there's the one, two, three categorization was --

MR. ANDRES: Was using humans in one, two for exposure.

DR. McEWEN: Yes, use in humans and -- yes, it was Part A in the Framework document refers to the importance of antimicrobial drugs for human medicine. That was the category one, two and three, in descending order of importance to humans.

And then, the Part B, refers to evaluating the potential exposure of humans and, as I understand it, that's -- well, as they outline the Framework, it's a -- contains elements of the drug attributes, the product use and applications and potential human contact of presumably resistant organisms, how they're shed, whether it's contamination of the food product, what events are happening to food as it goes to the food chain, extent of use in the population and that sort of thing.

So again, just in terms of the objectives, and I think this relates to what was said -- was it Bill Flynn when he talked about the rate and extent in terms of the -- as I understood it, the objectives of pre-approval studies was to evaluate the rate and extent of resistent enteric bacteria and evaluate changes in enteric bacteria in the pathogen load sort of concept.

I think that first one, evaluate rate and extent of resistant enteric bacteria is largely aimed at the sort of Part

B in the Framework document, the evaluate potential for human exposure.

So I guess in summation, the main point then is to supplement what Scott said about the classification of drugs with respect to human importance. We're also gathering information to deal with this extent of exposure.

MR. ANDRES: I guess would a better summation of both your points be essentially these studies would be used to where on that grid, that, you know, three across, two down, the product fits into, your comments about the human use and yours as to the extent and exposure?

DR. BROWN: I think the exposure is more driven by what the claims are for the actual product use, the indication. And I don't see these pre-approval studies addressing the indications nearly as much.

So I guess I take a little exception to Dr. McEwen's comment that these pre-approval studies are intended to also look at exposure because I think that really is driven more by the intended use of the product and -- I don't know -- Cathy, is what your comment --

DR. EWERT: What I wanted to clarify was that, the way the draft document is written right now, the drug is categorized according to one, two or three and high, medium and low prior to the initiation of any pre-approval studies. That categorization is what dictates which pre-approval studies we

have to do.

So these objectives to determine the extent of the exposure of the product, according to the way the document is written now, has to be determined before we can initiate the studies.

For example, a compound that's number one and a H, which would be high exposure -- that would be a feed medication or water medication, that would require both the resistance study and the pathogen load study.

If it's a one and an L, low exposure, pathogen load studies are not indicated right now. That's the way the Framework document is currently written. And Dave or -- Dave, either one of you want to comment more on that. So keep in mind that the exposure and the category are predetermined before we start the studies. That's the way it's written now.

DR. WAGNER: I believe that the intent right now is that the categorization would be established before the studies are initiated, that I don't think, at least at this particular point time, there's any desire or any interest in having it be flexible. That may come out of this deliberation but right now --

MR. ANDRES: I guess that's why --

DR. WAGNER: Yeah.

MR. ANDRES: -- the point that was made that we started off this session, we're not to reach a consensus.

We're just trying to get everybody's thoughts written down so when we go back in our group session tomorrow afternoon, and what I'm hearing here is that he's thinking should be open to interpretation.

DR. WAGNER: Okay. Well, I must have misunderstood what you said because I thought you said that it was going to be open to interpretation based on these pre-approval studies and I don't think the document intends that right now.

DR. BROWN: I guess I'd like to challenge that interpretation because I think that what the document does is it categorizes, based upon a class of compound and it categorizes based upon an expected type of use pattern.

All of the date you're getting from pre-approval, these pre-approval studies, will help you understand what the impact is of that particular indication for that particular compound and within every class of compound, or class of compounds, each compound is unique.

And so, I would argue that, almost like the MRL approach where there's a provisional MRL and then a final MRL, that there be maybe a provisional categorization and then the pre-approval studies that are done as a result of that can impact upon what the final categorization is, which to me is what also will dictate post-approval types of monitoring and surveillance and mitigating factors.

And to me, one of the things that we have to think

about is, you know, whether we decide or determine from this what kind of pre-approval studies we have to do based upon categorization.

Ultimately, the categorization is going to impact upon the surveillance and monitoring and some of the actions that potentially can be taken, post-approval. So I'd like to see some sort of use of these studies, not simply to describe what's going on but actually to modulate the categorization.

CHAIRMAN MORRISON: So Scott, you would like to see a categorization of drug based on impact of the drug's use, not necessarily on its pattern of use? So for example. you may have a drug that's used in humans and in food animals and it has zero, let's say zero, resistance to development and that should be in a low category, not -- based on that, not based on its use?

DR. BROWN: Yeah. I think --

CO-CHAIRPERSON SINDELAR: Can I just, please, I'm sorry, ask you to identify yourself each time you come to the microphone so that --

DR. BROWN: Sure. Scott Brown, Pharmacia & Upjohn. I really think that we need to be careful about the categorization that is a general categorization based upon a general class of compounds and a general use pattern when we're actually going to be acquiring data through this pre-approval process and then through post-approval monitoring that may shed

some very different light on it.

And so, if we're going to gather the data, there ought to be some decisions that are taken as a result of the data that will impact upon how the product is evaluated there subsequently.

MR. SCHUSTER: Dale Schuster, Schering-Plough. I would like to agree with what Scott is saying and maybe give a more specific example of why it's relevant. The categorization is based on mechanisms being able to induce cross-resistent to an essential human antimicrobial.

Until you do a pre-approval study, an appropriate one being maybe an in vitro study looking at MICs of resistent strains to confirm which if any mechanisms of resistent confer cross-resistent from the veterinary drug to the human drug, you may not be able to appropriately categorize the new veterinary drug.

So in that case, an appropriate pre-approval study would be an in vitro study looking at mechanisms of cross-resistance. The results would tell you whether it does or does not confer cross-resistance to an essential category one human antimicrobial.

DR. McEWEN: Scott McEwen again, University of Guelph. Just to follow up, I guess along the same line, it would seem to me -- I guess if the intent is to do a categorization on exposure before there's a request for

pre-approval studies, I guess you could do that on the types of use and numbers of animals to be treated and that sort of thing, but I think it would be hard to do for some of the other areas that listed in the Framework document and that's the extent of resistance that exists, the mechanisms of infection of -- cross-infection of animals and that sort of thing and I would have thought that some of the objectives that were laid out for us, I think yesterday in the pre-approval study, that's to determine the rate and extent of resistance in enteric bacteria really would add to that categorization of exposure.

So, I guess you could do -- I think you could do, before the pre-approval study, I could see you doing some elements of that but I think other elements, especially as it pertains to resistance transfer and so on would need to be kind of re-thought, at least, in the face of evidence from these pre-approval studies.

DR. SAGRIPANTI: Sagripanti, Center for Devices at FDA, and we have a little experience on categorization --- they don't have to do with this but there's a couple of things that maybe I would like to share.

First, there's two types of risk. One is type one. You can get your antibiotic in a category that is not precise or is not the right class. On the other hand, you have the risk that you can spend a lot of your energy and small resources trying to push your antibiotic in the most favorable

class, and still you're not going to have proof of producing enough data for what Agency usually look as the safety and effectiveness.

So, you have to ponder both things, and I think in the long run, all those --- companies maybe get favored, demonstrating that they are class two instead of one or three instead of two.

Overall, a lot of energy and money spent in this category five without really proving safety and effectiveness and in the long run, you spend a lot of money, more than if you have accepted maybe an imprecise class. Maybe it's not the one you like but you just go.

You know, somebody told you a class two and you say, oh, he's wrong, but still you go ahead. You do all the safety and effectiveness and in the long run you have a product in a market much faster.

For the Agency discussing or letting the sponsor to argue which class is he in or he is not, it becomes a nightmare very fast. So if you want anymore details, I have several products in that regard.

CHAIRMAN MORRISON: So Chuck is writing up there, the comment here being that we hope that these pre-approval studies will gather some information to influence the final categorization or the final category that the drug is put into, post/pre-approval studies.

So you do these studies; you do all the -- find out some stuff, and the proposal I hear is that that information might influence the category that the drug is placed into finally. Is that right, what I'm hearing?

DR. HOLCK: Tyler Holck, Novartis Animal Health. To me, the main question is, is the information that's gathered going to be used to limit the use of this drug or is it used to gather information post-approval?

So I don't think that we're -- are we down the road to the point where we've decided that they are to limit the use of these drugs or is it truly baseline information? And I'd throw it back to that discussion and I'd welcome any comments.

DR. BYWATER: Robin Bywater, Pfizer. There does seem to be a certain amount of ambiguity about the objective of the pre-approval process. I think we were told yesterday that it was not a pass/fail matter and it was essentially an information gathering exercise, because that was what I -- the message I took out of what was said.

However, what we heard this afternoon implied something slightly different, that pre-approval means it's part of the approval process and you better get it right or you don't pass. Can someone clarify that for us?

MR. ANDRES: We can go back to the transcript. I don't think I said, if you don't get it right, you're not going

to pass. I think, by the very nature that we've said it's pre-approval, it must be done prior to approval. Now, what those studies, or how they are used, is a different matter, and without being the true expert on this document, I can defer this to either Dave White in the back if you've got a better understanding, Dave, than I do, or Dave Wagner, you can step forward. And I see him back there grinning.

DR. EWERT: Cathy Ewert from Bayer Animal Health. Perhaps I can just clarify it by asking the question, will these studies be pivotal, which means that they are part of the approval process?

Do we need these studies to gain an approval or do they need to be done pre-approval for information gathering only? I mean, that's extremely important. If they're a pivotal study, that's paramount to the approval process. If they're pre-approval, information gathering only, that's a totally different story. So, that's the clarification I think we might be looking for.

MR. ANDRES: Dave, you got that answer?

MR. WHITE: Dave White, CVM. I think I'd like to add Cathy's comments to the slides, what we bring up as part of our group tomorrow because, you know, we need these types of answers, I think, and I'm not one to --

DR. EWERT: This has never been clarified for us -- and right now they are --

MR. ANDRES: Well let's throw it out. Why don't we throw it out there and see what the answers are.

CHAIRMAN MORRISON: Cathy, are you -- it's never been clarified by CVM. Is there one way or another you'd like it to be? Would you like them to be pivotal or --

(Laughter.)

DR. EWERT: Yes; I can tell you how we'd like it to be.

CHAIRMAN MORRISON: How would you like it to be?

DR. EWERT: Well, it would -- maybe I shouldn't speak, maybe somebody else that's not in industry, but if it's a pivotal study, that means that it's integral part of the approval process and you can't have an approval until that study has been completed and accepted by the Agency.

And there seems to be a lot of question. As Robin just said, yesterday we were told that it's an information gathering process, although that's the first time we had heard that. We don't know what the endpoints are for the study.

So if it's information gathering, that could be just a pre-approval exercise, baseline information if you will. But if it's pivotal, that means the study has to be accepted by the Agency and it has to be accepted with some sort of endpoints.

CHAIRMAN MORRISON: So you would propose that these studies be informational for the approval process?

DR. EWERT: Yes.

CHAIRMAN MORRISON: And that would be an objective of them that we would put up here?

DR. EWERT: That it could be informational -- information gathering would have to be done prior to approval, but the approval would not be contingent upon acceptance of that study.

MR. ANDRES: Is what I have up there the first bullet? Are these studies pivotal to the drugs approval or are they information gathering baseline info? I mean essentially, before you start discussing what are the objectives, you want to know -- whether we have to do them or not, that's fine, but if we have to get -- to use somebody else's -- the right answer, then obviously the approval hinges upon that, if they're considered pivotal.

If it's just information background, here's what the -- then that's a different standpoint. So, does that get what you're -- are these studies pivotal to the drug's approval or are they information gathering? Is there a better way to word it? I'm just here as a scribe.

CHAIRMAN MORRISON: What I heard -- that's the question but then I asked, you would like it to be informational, and to me that's your proposed objective, that these studies are informational for the approval process. Is there disagreement on that in the group?

MR. ANDRES: I don't know if we need agreement.

CHAIRMAN MORRISON: Okay. Then that's the statement, that these studies are informational for the group; that's an objective of the group. It's not pivotal.

DR. BYWATER: If you want it on the microphone, that's certainly my opinion.

MR. ANDRES: Well, here's a better -- I mean -- Chuck Andres again. If we're not going to -- I mean, you just said, is the proposal of the group. That to me makes it sound like we're all in agreement that this is what the group wants. If I just put down proposal was to make them -- a proposal was made to make them information gathering only, would that suffice as far as --

DR, EWERT: Cathy Ewert, Bayer Animal Health. You asked me what my opinion was and I gave you my opinion, but the question we should pose is, are these studies pivotal to the approval of a product or are they pre-approval studies merely designed to gather information? That's the question that needs to be answered, and I don't know if that's the consensus of the room or not, but that's something that does need to be answered. Dale.

MR. SCHUSTER: Yeah, this is Dale Schuster of Schering-Plough. I'm known for being independent and not caring whether the group agrees or not and I would like to say that it's my opinion that they should be information gathering only.

The reason is that, based on the discussions this morning and yesterday and the presentations, each speaker had on the order of over a hundred questions on how exactly you would do the studies, and there was a wide consensus that regardless of how you do the studies, they're probably not going to accurately predict what happens in the real world.

And in fact, there was a great deal of discussion that what may happen is an acquired resistance which you wouldn't even know existed until you're in the real world and you cannot do a study with something that you don't know exists.

It's my strong opinion that these would be information gathering and it's not possible to do pre-approval studies that are really going to predict accurately the rate and extent of resistance that would be seen after the product was released.

DR. BYWATER: Robin Bywater, Pfizer. I think we shouldn't forget that we're not starting from ground zero in all of this. Practically everyone in this room has been involved with the development of an antibacterial compound over the years, whether in the U.S. or Europe, and there have been pre-approval studies, if you like, of the kind of things that have been touched on the last day and a half, for all of these compounds, and I would say in all cases, they have been informational.

They've been used as part of the totality of the regulatory process. They've been weighed individually and in total and a regulatory approval either granted or withheld at the end of the day. And I think we shouldn't attempt to really start from scratch.

We should be looking at what at present has worked and has worked reasonably effectively. Maybe some people are not entirely happy with all of the products and all of the uses that they're presently reached, but they're -- we shouldn't necessarily have to get too far back in the process. We should start them from we're at and build on that.

MR. FONDRIEST: Steven Fondriest, Union of Concerned Scientists, and I just wanted to say, if the Food and Drug Administration has acknowledged that resistance is a problem, and this is a concern, this is supposedly the reason why this Framework is being developed, and if we are concerned about the rate and extent of antibiotic resistance development, developing these pre-approved studies only for the sake of gathering more baseline information makes me wonder where in the process then would, if the antibiotic was going to be prohibited or banned or restricted, where would that fall into this?

And so, to say that these pre-approved studies should only be for collecting baseline information, I would have to say I would have some problems with that.

DR. BYWATER: If you're going to then make this pivotal with a pass/fail, then you have to start setting thresholds for each of these individual tests that have been talked about. And we were specifically told yesterday that we are not in the threshold providing at this particular stage. We're setting criteria, whatever that exactly meant, but we were not setting thresholds, and there's no way you can have this process as pivotal and decision making without setting thresholds at the pre-approval process.

CHAIRMAN MORRISON: I'm trying to understand -- just a second, Scott -- Steven, on your comment, and I'm trying to put it in light of what I understand are the pre-approval studies, that after all these pre-approval studies are finished, is there then a decision whether the drug is approved or not?

Is that the pivotal decision, when all of the studies are done? Am I correct in that? I don't know. Cathy, do you know that?

DR. EWERT: By definition, a pivotal study has to be completed and accepted by the Agency before we can file for a new animal drug application. So that -- and as Robin has said, if it's accepted by the Agency, there has to be a set of criteria stated somewhere that the study can meet. For example, efficacy studies -- we have to submit efficacy studies and they have to be -- we have to show that our drug is equal

to or better than drugs that are on the market and we do that with statistical design and study design.

In these studies, there's no endpoint. We don't know what the outcome should be that we can measure and really a lot of the work that we could do would be descriptive at this point. And so, if it's a pivotal study, it has to be accepted and we have to have endpoints --

CHAIRMAN MORRISON: Okay.

DR. EWERT: -- to either meet or not meet.

CHAIRMAN MORRISON: And right now, what we've been saying, or what I've been hearing is that these studies are informational and they go into a body of knowledge which is interpreted at the end of the pre-approval process and a decision is made whether the drug goes ahead or not. Is that correct?

DR. EWERT: Well, we don't know how they will use these studies.

CHAIRMAN MORRISON: Right. Right.

DR. EWERT: What Robin is saying is that in addition to all of the studies that are necessary and required by law for us to generate, most pharmaceutical companies generate additional information that's not required by law but that corroborates the information that we need to make a decision about whether or not to move ahead with the development of the drug. Is that what you're saying, Robin?

DR. BYWATER: Nodded affirmatively.

DR. EWERT: And so, at this point, if the studies are information gathering, certainly if we saw that there was a problem, that would be an internal decision, whether or not we'd want to even move ahead with the development.

But if -- and I keep going back to this -- without some kind of guidance on what the measurements will be and what the criteria are, I don't see how the study could be determined as pivotal right now.

CHAIRMAN MORRISON: And Steven, you're saying, I would like at least one of these studies to be pivotal, not the body of knowledge?

MR. FONDRIEST: No, I probably wouldn't go that far at this point, to say that I would like to see these pivotal, but it is that question of, how will FDA use this information? When will they -- how will these studies be used? When will they make their decision?

And I'm not quite sure that's been addressed yet.

I mean, I don't work for FDA. I'm relatively new in this -- working in this area, also, but to -- I'm just -- I'm wondering where in the process will a decision be made.

Has FDA even established a policy to incorporate this -- the pre-approval studies and the framework into the decision making process of registering or not registering new antibiotics?

CHAIRMAN MORRISON: Okay.

MR. FONDRIEST: And it would be nice to know.

CO-CHAIRPERSON SINDELAR: Steven, let me just clarify -- are you saying it's like a -- we are inviting, you know, your suggestions, your proposal. And what I'm hearing is that you're trying to establish safeguards here and that this information, if the information were such that it would pose a hazard or, you know, are you thinking that it could be used as a reason why the FDA would not approve a product?

MR. FONDRIEST: I'm concerned about the process and I'm uncertain about how it would be used and so I'm just raising the point at this time, that questioning whether or not is baseline or is -- the issue is, are these pivotal studies? Are we concerned about -- that's the question that came up and one answer was, I would prefer to see these as baseline only.

I would just raise the concern, before, without understanding how FDA is going to use this information, I wouldn't like this group to say only that these can be baseline information, that I think we need more information to see how the system is going to use this information to begin with.

And I'm not quite sure -- perhaps someone could tell me how that will be used or if it's even been thought through at this point.

MR. ANDRES: Chuck Andres, again; CVM. Let me kind of do just a quick backtrack. We had a presentation yesterday

morning on the history of 558.15, the whole salmonella shedding, and what that study was a pivotal study for new antimicrobials in feed and water that came through.

That now, in light of the resistance issue that befalls us today, I believe that much of what we're discussing have been discussing for really a couple of years now is that's not getting us what we need -- is what we're doing now, attempting to rewrite that in a broader sense so that it goes to all food animal antimicrobials.

I'm posing a question; I'm not making a statement; I'm posing a question. And, if we're not doing 558.15 studies that address salmonella shedding which, okay, then what are we doing? And I don't know whether that addresses, ultimately, your question, Steven, of how will it be used in the Agency, as a pivotal or not.

Certainly those studies were pivotal as far as is puts sponsors into different directions depending on the outcome of those studies. It may not have left them with, well okay, the drug's dead in the water because of these results, but it certainly led the Agency, gave them information, well, where do we go from here now with the study given the results from the shedding study? I don't know whether that I see -- but I don't know the exact answer, either.

CHAIRMAN MORRISON: Scott.

DR. McEWEN: Yes, we've got the Scotts here. Scott

McEwen, University of Guelph. I just would day, those of us who haven't been involved in the drug approval process, we don't have the jargon, I guess, and so the implications of pivotal and so on for information only escape me a little bit.

I was a little worried when I heard, if only -- only for information purposes. That implies that the information could not be decisive, I guess. And, I felt better when Robin described it as, we take the information and put it in with the whole package and then make a judgment on the whole package. Intuitively, that seemed fine with me.

And in some instances, you could imagine the scenario where the pre-approval studies would be decisive when you look at the entire package and all the information together. But, where that fits in with pivotal and for information only, I'm not quite sure.

But I like the concept of, we'll take this as one set of information and we'll put that together with other information and we make a decision on the whole.

DR. BROWN: The other Scott. Scott Brown, Pharmacia & Upjohn. I understand the need to have some utility to these studies and, in fact, I have a philosophical problem with gathering information just for the sake of gathering information.

But I guess I'd like to propose, not for this group to try to decide, but for an item to be done is to have a real

clear decision tree on how decisions are going to be made and whether these studies are going to be part of that decision tree or not.

Now one of the decisions that is now in place, at least my understanding is it's in place as a result of these changes and the Framework document that was not in place when the 558.15 came along, was the opportunity to take action, post-approval, prior to a point where there would be an imminent hazard declared.

And my understanding is that there is now the post-approval opportunity to take other mitigating actions which would be up to and including the removal of the product from the marketplace, depending upon what the surveillance and monitoring data are.

So I think that the decision making process prior to what we now feel like we're within was really decidedly pre-approval because the legal aspects of removing a product from the market through imminent hazard was onerous.

And so, the opportunity of 558.15 to be a watershed kind of a study, I think now needs to be taken in a different context, but I really think that we ought to be, and I'd like to see this as one of the things that comes out of this group, is a strong challenge to the Agency to have a clear decision tree on how these studies are going to be used.

And I really do agree with Steven that there needs to

be some understanding of that. It's something that we, as a pharmaceutical industry, have been wanting to have for a number of years, to know how these are being used and what's the decision making process?

It needs to be clarified because at this point, we're not sure how these studies are going to be used. And I have, again, some philosophical concern about gathering information without any ultimate decision making because there will be people who will choose to make their own decisions based upon those data, regardless of whether it's in the regulatory framework or not.

DR. MUDD: My name is Tony Mudd and I'm here representing the Global Animal Health Industry, COMISA. I think the difficulty we've got ourselves into here, deciding whether these should be pivotal or merely for information purposes, is we don't really know as yet what these studies should be, and I feel that until we have better definition of precisely what sort of studies we really are talking about, then and only then can we decide whether they are going to be pivotal or not.

CHAIRMAN MORRISON: So there's concern about the process and where these pre-approval studies fit in the process and how these studies are going to be interpreted, the decision matrix for making the decisions and knowing those two things then would help you determine the objectives of the studies.

In general, what we heard was, one of the objectives of the studies might be to provide information for the final categorization of the drug, if there was going to be that ability to influence the categorization of the drug.

Are there any other objectives that you could foresee being learned in these pre-approval studies? And I guess -- is this a point maybe to discuss Fred Angulo's five points, are they possible? Bill Flynn suggested, you know, if you want to go into the five points that Fred suggested we could or if you've got some modification of it, that would be fine, too.

DR. McEWEN: I guess my feeling while I'm here is that while I agree with those items, and I would add the components that are necessary for rethinking, perhaps, the categorization of exposure, but those in essence, I think, are components of the point you just made about what the categories for human health hazard are and what the categories for exposure are but adding some elements of specificity in terms of what kinds of information should these studies be designed to detect and measure. And, I guess I felt that the points he raised had merit.

CHAIRMAN MORRISON: Do you want us to restate what those five points were and go through in detail or -- it might be a reminder for us.

DR. McEWEN: Well, I would think so, if there's no objections from the group. Do you guys have them or do you

want --

MR. ANDRES: I think we're going to need to get them.

CHAIRMAN MORRISON: I don't remember what they were.

DR. McEWEN: I think, from my rough notes, it was mutation rates of genes, presence of resistance genes to these drugs. I think presumably you meant they're already existing in bacteria of interest, frequency of resistance elements and determining optimal dosage rates or dosage regimes, rather.

MR. ANDRES: Frequency of -- step back.

DR. McEWEN: Sorry.

MR. ANDRES: Frequency of -- I'm not a fast typist.

DR. McEWEN: Frequency of transfer. We should get Scott up here to type; he's fast. Frequency of transfer resistance elements and determination of optimal dosage regimes, I think, was the -- to decrease resistance rate.

And the other one, I've got kind of messy notes here, but it had to do with potential for selection through cross-resistance with -- so in other words -- to paraphrase it, it was, what potential is there for this drug to select for resistance to drugs important for human treatment. We need a bullet phrase for that one.

CHAIRMAN MORRISON: Does anybody have Fred's fifth point?

VOICES: (Simultaneous responses/not near microphone.)

CHAIRMAN MORRISON: I thought it was, too, to categorize drugs.

DR. McEWEN: Categorize -- so that's --

MR. ANDRES: Mutation rates --- resistance.

DR. McEWEN: Okay. So if the last one is categorization of drugs, he was thinking, I think, of categorization in terms of human hazard. I would add to it the categorization for exposure as well.

CHAIRMAN MORRISON: Well starting from there, assuming or not assuming those are right, but what are some people's comments on that?

DR. VAUGHN: Michael Vaughn with Bayer. As we bring up these points, and I have a question for everyone in the audience, is the technology readily available to do this, to answer these questions today?

DR. BROWN: Scott Brown, Pharmacia & Upjohn. Certainly, the first one, the second one, the third one, and arguably the fifth one, if you're looking at cross-resistance, are relatively straightforward and things and things that typically we're already doing.

The one that I have some concern with and probably more because of my pharmacokinetics background and so forth is determining the optimal dosage to decrease resistance. I think if that is -- if the decrease in resistance is intended to have the implication of the zoonotic organisms, and I'm not sure I

know how to optimize dosing which now has a twofold purpose -- one is to enhance or improve efficacy and the other being to minimize resistance of a completely different pathogen or another organism that is arguably an innocent bystander in that particular target species.

I think it's a whole lot easier for us to look at trying to find a dosage that enhances or improves efficacy and diminishes the onset of resistance in the target pathogen because I think those two are much closely linked and there's a much greater likelihood of being able to pull those things together. I don't think the technology exists right now to optimize dosing for efficacy and for minimizing the development resistance of zoonotic organisms.

DR. BYWATER: Robin Bywater of Pfizer. I was going to make much the same point as Scott, that these are, with the exception of number four, fairly straightforward exercises that, as he says, are regularly carried out.

I'd look at number four; I wouldn't want to get rid of it because I think determination of the optimal dosage ought, as a corollary, to carry the benefit of minimizing resistance. If you've got the optimal dosage in terms of efficacy, I think it's probable that that will likely to be the optimal dosage in terms of reducing resistance.

If you're taking into account the fact that you don't want to overdose, you want to use the minimal amount of

antibiotic to achieve the best cure you can get. And so, it's a difficult one to actually link in hard terms, an optimal dosage in terms of decreasing resistance, but if you optimize a dosage, then you should get that benefit anyway.

CHAIRMAN MORRISON: So we've heard that there's technology available for one, two, three and five, and four would be difficult to do, today.

DR. VAUGHN: Michael Vaughn with Bayer. What is the impression of the group, as Fred presented these ideas, would they be information gathering or would they be pivotal?

(Laughter.)

DR. SAGRIPANTI: Sagripanti, Center for Devices. I have a question about one which is a mutation rate, you know, for resistance. I think I understand that was in vitro, of the determination, for which I had a long conversation with Lipsitch after all, and he couldn't -- I say, haven't been able to relate those rates for mutations with anything happening their population -- in this case, humans, but I would imagine in animals the same.

So my question is, what is the value that you give to these numbers which of course are going to be very costly to obtain? If anybody can answer that, I appreciate it. It would be nice if we have a number that relates, ten to the five here equates to ten to the one in the dynamics of the population of animals or whatever.

I haven't been able to obtain that number and in talking to Lipsitch this morning, he hasn't been able either. So I question the relevance until we get some number that would mean something.

DR. BROWN: You bring up a really good point which I think may be something we need to look at for all of these things which is some degree of controls, positive or negative controls.

An example for the mutation rates would be that we know what the mutation rates are for some of the other compounds in the same class, and if you look and see how it compares to what is already existing in the class, then you have a frame of reference.

I do agree that you need to have some kind of reference point or controls for some of the things like the transfer resistance and so forth; there may be some other ways to do it. We know there are some compounds that are out in the marketplace that are notorious for causing resistance to occur very rapidly, Rifampin being an example of that.

So maybe you could use Rifampin as a positive control for resistance onset and then have something else that would be known to not generate resistance nearly as frequently. But the point is well taken, that there needs to be some real clear control elements so that you have a frame of reference for how to interpret these things.

CHAIRMAN MORRISON: These objectives were suggestions by Fred, and then we said that -- so we listed them and then we said that at least four of them we think we could do. They're technologically available, we could do them. Is there at least one person in the group who would say yes, and I think we should do these four or five? Otherwise we've just listed five of Fred's ideas.

(Laughter.)

MR. WHITE: What's the alternative?

CHAIRMAN MORRISON: None of them. I mean, if you don't say anything, then we wouldn't put any of them as objectives.

DR. HOLCK: Tyler Holck with Novartis. I'd go back to what Scott stated earlier, where would those fit into a decision tree? And if you can't answer that question, then I fail to see their usefulness.

DR. McEWEN: Scott McEwen, University of Guelph. I guess since I suggested we consider them, I just better speak to this. I think that, in the sense of, as Bill Flynn talked about, these pre-approval studies being designed to determine or help us gather information on the rate of resistance and transfer and that sort of thing, that these fit within that, so I think they're logical points to address in terms of gathering information on resistance risk of these drugs.

How they get used is -- we already agreed that the

Agency should clarify how this information is used. So if you're looking for somebody to say that these seem reasonable, then I'll say that.

DR. BYWATER: Robin Bywater, Pfizer. Just a comment on this term "decision tree." That bothers me, rather, because it does again imply that there are nice, clear criteria for pass/fail, go left, go right, go back to where you started. So in that sense, I don't think decision tree is necessarily the right word.

In Europe, we have a system and I mean, I don't want to complicate the issue by saying how we do things elsewhere, but this would be part of a safety assessment of a drug which will be taken together with residues and toxicology and all the rest of it, and a crucial part of the European process is an expert assessment where all the data is looked at as a whole and assessed and the expert arrives at a conclusion which then goes to the regulatory authority which they may or may not accept.

So, that's where I see these kind of data. And they are, I think, relatively straightforward data technically to obtain. They're not vastly expensive and they are the sort of information that I think companies would themselves want to know about as well as presumably the regulatory authority.

MR. SCHUSTER: Dale Schuster, Schering-Plough. Could you put the five points back up again, please?

MR. ANDRES: Sure.

MR. SCHUSTER: I agree with my colleagues that the four that seem to be technically feasible is true, but there was a couple of points I wanted to make. For instance, depending at what level you envision these studies -- for instance, pick number three, frequency of transfer of resistance elements.

If that's done in rather simple methods in vitro, that's true. If you want to ask that question in vivo, I would argue that the answer is not true. In fact, there is no standard protocol in which you would identify resistance transfer in vivo. That would be predictive of what you would expect in the real world. So there are some caveats to that.

CHAIRMAN MORRISON: So you would suggest just stating in vitro frequency of transfer? Is that maybe the intent of others? Yes?

VOICE: Yes.

MR. SCHUSTER: Some of these, and I'm not sure of Fred's interpretation, but some of these might be very much in vivo studies which I think would be subject to all the questions that were raised with animal studies already.

So in the simple sense, these are true. I would also like to point out the caveats that some of these really have tenuous relevance to rate in extensive resistance in the real world.

For instance, mutation rates of resistance, it's nice to know what they are, but in some cases, they're far different than what really turns out to be the case in the real world. So there's some caveats on how useful these things are.

It's my opinion, yeah, as a first start, that would be the sort of thing you would want to do, but there are a lot of caveats that go with them. Something else that you could add as maybe a sixth item that could possibly be done would be MIC testing to zoonotic pathogens.

Typically we do MIC testing to the target pathogen and it's required and it's straightforward and it's standard, but there may not be any information provided or generated on the MIC of something to say campylobacter because it's not a target pathogen.

That's some more information that could be done in a pre-approval study. It would certainly be relevant to surveillance and it would be interesting and straightforward type of study that would have some meaning.

DR. SILLEY: Peter Silley, Don Whitley Scientific. I think just the point that was made earlier about doing these in vitro resistance studies, which was they are straightforward I think is the point Scott has already made in terms of having controls and positive controls in there.

Because in the same way that we've heard over the last day and a half that depending on the protocol that you

actually use, then you can affect the results. So I think it's important that we do have those positive controls.

I think, also, the point about the in vivo transfer of resistance, then yes, there are techniques available to do that, but generally they would be in sort of germ-free animals. They would certainly not be, in one sense, out in the field; they become incredibly difficult and incredibly complex.

And again, I think even if we use an in vivo model, which is not a field situation, then we're getting also a very artificial situation. So I think it's important that we do realize you can do in vivo --- transfer of resistance studies, but I don't believe their relevance is particularly significant because we just do not know how that relates to normal animals out in the field.

MR. MATHERS: Jeremy Mathers, Alpharma. I'd like to echo the point that Dale made a few minutes ago. In terms of the in vitro studies, I think they should be viewed with caution. It's good that things are being done in vitro and on a molecular basis; however, you're starting to imply then that -- you're implying thresholds for resistance elements in vitro which may not apply in vivo. That's one point.

The other point is the existence of the pre-existing presence of genes in the environment or elsewhere should not preclude, or it should not be a pivotal fact which would exclude a drug in all cases. Thank you.

CHAIRMAN MORRISON: I think Jeremy, you're saying, if I understand right, you're concerned again about how these studies will be used, the decision making process and that influences the objectives. Yeah.

Any further objectives that you'd like to put up or that could be done if you had confidence in the decision making process before we move onto a working break where we go to the first question? And I'll just remind you, this is for input. You don't have to agree to everything. Right? Okay.

Then Aleta, should we take a working break whereby if people want to use the facilities, grab -- is there a pop over there or something and we'll start thinking about the first objective, first question?

CO-CHAIRPERSON SINDELAR: I'm sorry; they were supposed to set up here -- I believe there's a table set up right behind us, outside of the Twinbrook Room, so please help yourself. Otherwise, go ahead and you can step back outside the Regency but there is a table that's been set up outside the Twinbrook Room with refreshments.

CHAIRMAN MORRISON: And figured out or got some information for the process and he's going to tell us what it is.

MR. ANDRES: I posed the question that's been a stumbling block for us here because we can't get into what type, what should the studies look like and how should they be

designed and so forth because everyone wants to know, well how are they going to be used.

And I went to multiple sources that I have highest of confidence within CVM and the answer is yes, they will be pivotal, pivotal in the sense that they will be used as part of our decision making process to approve or not approve the product.

If you use the analogy, not everybody that brings a product in has to do a full tox package. You may look and the drug has no residue. Well, that's part of the decision making process. We go step-wise, what are the results and make a decision, where do we go from here?

A similar process than this and that these studies, study, studies, will be used in helping us determine, where do we go from here as far as what's going to be "required" from the drug sponsor in order to make us satisfied and give us the information necessary to determine that the drug is safe?

So when we start talking about is it pivotal or not, certainly I could give a number of examples, not specific ones but generic ones, in which studies which the sponsor has declared non-pivotal for animal safety purposes.

You know, they're either, you know, university -- I don't want to pick on universities, but university studies or ancillary studies to do research on, and we have used those as the basis for requiring drug sponsors to go out and investigate

adverse drug events.

You know, your product looks like it increases this. Well, that study now, that "originally declared non-pivotal study" is a pivotal part of our decision making process of why are we requiring you now to do a more formal pivotal study to address a concern that, you know, why did ten percent of the animals in the study die when it's supposed to be a, you know, production drug. It's all in the treatment.

So if we can get past the, are they pivotal or not, the studies will be used as part of the decision making process and however you want to interpret that. And if we can move on with the, really the first question.

CHAIRMAN MORRISON: So every study that you do is a potential deal breaker, so to speak, or you wouldn't do it.

MR. ANDRES: Same reason why sponsors would decide a go/no go as they get down to, you know, the decision tree of whether to continue with the -- to continue developing a drug.

If you go to, let's see -- if you go to Fred's points and I would have probably hazard to say if you did -- if you're able to do all five of these, and all five of them lit up the tests, probably a bunch of you would be making the decision, we're probably going to pull away from this drug.

We probably ought to rethink. So, why isn't that type of information important on our -- from CVM's standpoint

of decision, okay, where does CVM, in its assessments of safety, need to go from here? And I think that's how this information is going to be used. And with that, I'll shut up and start typing.

DR. VAUGHN: Michael Vaughn with Bayer Animal Health. If in fact these will be pivotal studies, then we have to know, in industry, what the criteria is that you're going to use, CVM is going to use, as to whether this is good or bad or pass or fail. That'll have to be defined with those various parameters, and so we have to understand that.

MR. ANDRES: Chuck Andres again. That's why we're here. That's why we're asking you these questions, what -- you know, what are positive aspects? What objectives should be part of these pre-approval studies so you can help us develop this requirement. So and until we get past that, we're not getting anywhere.

CHAIRMAN MORRISON: So we sort of spent some time, then, defining that each study is important and we then put up five objectives, four of which we felt were achievable, technologically, and so we've done that. Are there any changes you want to make to that and before we move on, not that you agree with all of them but those are input ideas, again, for CVM as far as objectives of these pivotal studies, pivotal pre-approval studies? Okay.

The first question that we've been asked is to --

from the study concepts that were presented over the last day and a half, from all of those studies that were presented, what are the positive aspects that have occurred to you? And within that, we'll get to, what were some limitations that occurred to you?

Can the approach, approaches, or any one approach predict resistance development as you listened to some of those studies, mathematical models, in vitro models, in vivo assessment, etcetera? Can any one of those studies predict pathogen load?

That's all sort of within the first question -- out of all these studies and ideas that you've listened to over the last day and a half, positive aspects, limitations, are they predictive, what were your concerns or thoughts?

DR. BYWATER: Robin Bywater, Pfizer. One positive aspect was the recognition that the existing method of trying to assess pathogen load, that's to say the salmonella excretion, have been largely a waste of time and effort and that this whole question should be perhaps be open as to whether or not pathogen load type experiments should be eliminated from the process.

And that seems to be an important question which we should address and, speaking personally, I don't think it's a measurable concept and therefore, we probably should drop it. But it does raise another question.

I mean, that's an integral part of the Framework document, how sacrosanct is that Framework document in every line? Is it a guidance? Is it an instruction? What flexibility do we have to either respond or not respond to what's in that document?

MR. ANDRES: Chuck Andres, CVM. I think, if you recall, it was put out for public comment -- when was that? I can't remember the date. Our own regulations require that we put out documents for comment. We have not final -- it's still in draft form, so my assumption would be that it is changeable.

DR. McEWEN: Scott McEwen, University of Guelph. I don't have strong feelings on the pathogen load thing, but unless I missed something, I didn't hear data or see data presented that convinced me that the pathogen load notion is a waste of time and not worthy of further exploration.

I know from some of our own research that one of the important parameters that contributes to the risk of food-borne disease to people is the prevalence and concentration of food-borne contaminants at various times within the food production and processing system.

And so, I agree that there's lot of questions around it and how you would do it and all that sort of thing, and questions about whether it might be worthwhile. But I just didn't see the data presented that convinced me that it's not.

MR. ANDRES: Is what I have up there now, because

that's -- I mean, that's effectively what 558.15 required, was a shedding study, and I think the whole discussion, the Framework document and so forth, its creation, was born out of that that was not going to be adequate.

DR. VAUGHN: Michael Vaughn with Bayer. Scott, I don't know that it was the intent of any of the presenters to present defining data to defend or not, but I think there was enough information from enough people who have dealt with the pathogen load studies throughout the years that we need to seriously consider as a group to suggest that it shouldn't be a part of the pre-approval process.

Even though data wasn't presented, there was enough information from enough experts that had been involved with it that I think we ought to consider as a group to suggest that it be done away with.

VOICE: Should be what?

DR. VAUGHN: Done away with.

DR. McEWEN: Scott McEwen again. I guess the statement that the existing method is not adequate is a lot different than saying there shouldn't be anything on the pathogen load. The first statement says that if it's not adequate, that means that making changes to the system is an alternative, stating that pathogen load is not an issue that should be considered and it explicitly says that it shouldn't be part of the process.

CHAIRMAN MORRISON: You're saying, Scott, that there's merit in measuring pathogen load as far as a drug's pre-approval process is concerned?

DR. McEWEN: Well I don't know that I know enough about it to say, categorically, that it is. I would just say that I didn't see the information that convinced me that it's not worth considering.

I think the notion that -- conceptually, I think it's possible that use of a drug would alter the gut flora and knowing that the prevalence in concentration of enteropathogens being shed in feces is a risk factor for contamination. That says to me that it's worth having on the table, but I don't have the design of experiments here that would, you know, definitively answer that question.

I guess what I'm saying is that I didn't hear the evidence that convinced me that it's not worth even considering and that -- so I would sort of buy into the first statement that exists -- you know, it sounds like the people working in the area, both in the Agency and others, that the current system is not adequate, fine, but that suggests that it's possible to modify the current system into something that is adequate.

MR. ANDRES: Chuck Andres. Would it satisfy both parties, if you will, if both of the positive and as a limitation, I'll put under the positive that -- again, we're

not trying to get consensus.

We're trying to get all thoughts down, what everybody's viewpoint is, and under one positive aspect might be, Scott, yours, pathogen loads should be considered and I can put under the limitations, they should not be considered.

I mean, I know that's redundant, cancel each other out, but when we sit and deliberate and present this tomorrow, it's an accurate reflection of what we discussed.

VOICE: (Away from microphone.)

DR. McEWEN: So the question was, is that first one all right? Again, I didn't really see the data that -- where you could say that it's not adequate but, you know, I take the word of the FDA scientists and the scientists with the industry that say it's not working and it's fine as it is.

But to then categorically exclude pathogen load from consideration, I personally couldn't endorse that. So I would go along with -- take it on good faith that the scientists working it are not comfortable with the current procedures.

MR. MATHERS: Jeremy Mathers, Alpharma. I just wanted to mention on the 558.15 studies, I had a chance to review a couple of those before I came to this meeting and it wasn't simply a salmonella shedding study.

They did look at some of the native E.coli flora for some of these studies and resistance frequencies over a course of time, the treatment versus control. So I think there were

some positive things and through our historic -- our literature references to resistance frequencies that could be a guideline for reviewing some of these aspects. Thank you.

DR. SUNDBERG: Paul Sundberg, NPPC. Rather than talk about whether pathogen loads should be part or should not be part, pathogen load is a discrete section within the framework and maybe a suggestion from this group would be for -- since this is input to CVM, that CVM conduct the workshops.

Although we all enjoy coming to these things so much to talk about those discrete sections that may be worthy, since it is a part of the Framework document, and there's some difference of opinion of whether or not that would be a piece that would be used to make a decision, that would seem to me that one of the recommendations would be, let's specifically have a workshop on pathogen load where we can decide whether or not it's feasible.

If we don't have the information at this meeting to decide whether or not it's feasible, at some point we have to make that decision.

CHAIRMAN MORRISON: Chuck, maybe we can start a slide somewhere for just general comments and put that one somewhere.

MR. ANDRES: Okay.

CHAIRMAN MORRISON: Dave.

MR. WHITE: Dave White, CVM. General comments for both -- for Scott and Robin as well, in terms of -- do you

remember yesterday when Jean Cooper, she did say, actually, some antimicrobials did fail based on the old 558.15, and they failed through because they increased salmonella shedding, so there is some merit to these studies.

I think that the way they're designed now, they are inadequate. And, can we take this template and make it better to address the concerns we have today?

CHAIRMAN MORRISON: Other thoughts, as we look at that question? Positive aspects of what you learned or heard over the last day and a half, limitations, concerns? Can the approaches that were discussed predict -- how predictive are they, do you think, of resistance development?

DR. McEWEN: Scott McEwen again. I wonder if there would be any merit in listing the different main categories of study concepts. I wasn't quite sure what's implied by that.

CHAIRMAN MORRISON: I asked, because I had the same question, and so I asked Bill, and Chuck, you make sure I get it right or wrong, and he said, well, whatever you heard over the last day and a half, these different presenters from different areas and so on and so forth, that's what the study concepts means.

MR. ANDRES: I guess the thought was that just listing them might add some structure to the -- maybe listing pros and cons of the main approaches. You mentioned, I think, some of them, Bob -- the in vitro studies, mathematical

modeling, animal experiments. Fred and others introduced the idea of field studies involving real world scenarios.

CHAIRMAN MORRISON: Yeah; I listed a couple, if you would. So there was mathematic model. What were the other ones? There was the --

MR. ANDRES: Well, I invite the input from others, but there was the -- we had the mathematical modeling which is the sort of population biology approach from Mark Lipsitch today.

We had the use of in vitro studies from Dr. Kotarski on the -- looking at sort of in vitro simulations of gut eco systems. We had discussion yesterday on animal experiments, the -- I guess along the lines of the 558.15 studies and, do we have anything else?

And then, as I said, Fred brought up the suggestion that I think others had in their mind of the possible utility of -- on farm studies or real world scenarios as opposed to a contrived experiment. And I'm not sure if the pharmacokinetics, pharmacodynamics elements are a subset of those.

CHAIRMAN MORRISON: And MIC --

MR. ANDRES: Right.

CHAIRMAN MORRISON: -- testing. Well, to start if off, did you have any positive views, concerns, negative views about the mathematical modeling, for example, the Harvard

Business School presentation, the herpes virus and doing a mathematical model to predict out in the future on resistance?

DR. McEWEN: Scott McEwen again. In terms of the positive aspects of the modeling, I think the -- it enables -- in theory I mean, it enables you to test hypotheses about events that would be impossible to set up in a controlled experimental situation involving populations of animals and/or people, so there's benefits to that. We can look at the possible effects of interventions and that sort of system as well, so there's some advantages.

CHAIRMAN MORRISON: Would you ever see a mathematical model as being part of the pre-approval process that the company has to present a model?

DR. McEWEN: Well, in practical purposes, I think we're a long way from that because we don't have the tradition in the veterinary world, or I think in the various disciplines that sort of partake in the process, that we don't have the traditional -- the tradition and the training and the expertise, I think, to really do that today.

I think that may be something that's useable down the road in general. We do have modelers in population biologists that have certainly worked in other areas and that expertise could be brought to bear here but I wouldn't see it happening tomorrow, frankly. So I think that there are decided advantages.

The disadvantages that I see right off the bat are that the expertise issue, it's in short supply. Mark outlined a number of these things in his talk. They tend to be a general demanding of data that are often sparse and they require assumptions to be made that are open to challenge.

There's a communications difficulty because most people don't understand how they're done and there's a reluctance to sort of believe in things you don't understand. So, I think they have their place but there are downsides.

CHAIRMAN MORRISON: Based on what you heard over the last day and a half, do you think that we could design pre-approval studies that would predict, somewhat accurately, resistance development in the field?

MR. SCHUSTER: Dale Schuster, Schering-Plough. One thought I had on the mathematical modeling would be that it could fit into a risk assessment to indicate which types of drugs and uses might need further pre-approval studies, not to be submitted so much by sponsors but for FDA to put into risk assessments to sort out which issues need to be addressed and which ones are probably not of concern.

DR. SILLEY: Peter Silley, Don Whitley Scientific. I think with all models you need input parameters and I think the problem is that obviously if you're talking about new compounds, you've not got many of those inputs that you

actually need to then begin to do the modeling. I think it's a difficult scenario to envisage that that could be something that one could take at that very early stage.

CHAIRMAN MORRISON: Do you think that those objectives that we said earlier, those four or five objectives, if we could study design studies that would address those objectives, would they, with some reasonable accuracy, predict resistance development in the field?

VOICE: (Question/away from microphone.)

CHAIRMAN MORRISON: Yes; if we were to do four of those five, the number four was with regards to optimum dosage determination, but if we could do four of those five, would those help us screen or screen out or kick in drugs that are a problem for resistance development in the field?

DR. BYWATER: Robin Bywater, Pfizer. Although I'm supportive of the fact that these studies should be done where possible because they have basic information, I don't we should over anticipate the use in predicting exactly what's going to happen in the field.

I was bothered a little bit when you said if you've got a positive result in all of them, then that would be a reason to say no, because the fact is, you will find resistance. You will find genes. Those genes probably will be transferrable. Then it comes down to what are the genes?

What's their significance in terms of the human situation

and how often it occurs, and to be actually predictive of how often it will occur in the field is going to be extraordinarily difficult. And so, I think we shouldn't be too -- have too high expectations as to the ability to predict what will happen in vivo.

DR. SILLEY: Peter Silley again. I think I would support that completely. I think those in vitro studies do show they put some numbers and to begin to maybe quantify to some extent the potential for that to happen, but they don't tell you anything about -- necessarily about the likelihood of it happening in the field.

And I think if one looks back historically at some of the compounds that are out on the market and if one were to then look at the sort of data that we're talking about now that was generated for those compounds, I think you'd find it very difficult, then, to actually use that information to predict what has happened subsequently.

And I think as Robin rightly said, we know that it will happen. We put some, maybe some numbers against it, but it doesn't tell you anything about whether it actually will happen once you actually get out into the field.

DR. BROWN: Scott Brown, Pharmacia & Upjohn. I guess the only thing I would add to it is that I do think that these four or five things can give you almost some sort of a vector analysis of whether you need to have a higher degree of

scrutiny, post-approval or not.

I don't think it will accurately predict what will happen post-approval, but I do think it can give you some sense of whether you need to maintain a high vigilance or whether the vigilance can be modulated a little bit. That perhaps would be the only thing I would see.

And I think in Dr. Lipsitch's discussions about the mathematical modeling, his comments were that because of all the assumptions that were made in there that one of the best uses of the kinetic approach, if you will, is to sort of raise an awareness of what some of the possible outcomes might be.

MR. FONDRIEST: Steven Fondriest, Union of Concerned Scientists. In terms of the question of whether Fred's four or five, and I think possibly five, all of them have utility in determining or assessing the development of antibiotic resistance in the field, but I think one piece of information that we're lacking, one piece of information that FDA is lacking and doesn't have, is actually the amount of the antibiotics that are being used, either as -- either in the subtherapeutic or therapeutic levels and without that information it would be very difficult to truly assess the development of antibiotic resistance.

And with that -- and so, I would just say FDA needs that information, and as far as I understand, they have no mechanism to collect that information and to use that

information in terms of its development of risk assessment with antibiotic resistance.

DR. BROWN: Scott Brown, Pharmacia & Upjohn. In response to that one, I guess I need to make sure we're still talking about the same thing and that in this case is pre-approval studies and whether we can predict what happens post-approval.

It's equally as impossible for us to predict the magnitude of use of a product, pre-approval, for a post-approval situation. Compound that with the fact that once a compound goes off patent, that there are potentially generic competitors that can play a role as well.

And I think, at least in the pre-approval context which we are in right now, providing usage data, is at best a swag and also fraught with those same assumptions that cause such a difference in the predictive ability of those mathematical models that Dr. Lipsitch was talking about.

DR. BYWATER: Robin Bywater, Pfizer. We should remember that what we're talking about here, initially anyway, are these being applied to a new compound, possibly a new category of compounds, which simply aren't being used in the field; and therefore, you're having to try and guess how much might be used when eventually, if eventually, it gets a regulatory approval.

So I don't think it's really a key part of a new

process and to make some prophecy as to how much you'll sell. As a drug producer, you hope you'll sell rather a lot, but you're never quite sure.

DR. McEWEN: Scott McEwen, University of Guelph. But again, the components of the concept of extensive use that would be part of the classification for potential exposure, and that is, is the drug intended for individual treatment of animals on occasion or is it intended to be used in a more widespread basis? I think there could be some qualitative differences or components with respect to amount of use made there.

DR. SAGRIPANTI: Sagripanti, Devices again. I think if any of us is put in a room for a while and asked to come out with four or five things that we would like to know, I think, independently, we all would come with some sort of collection of things.

Some of us would include the amount of the kilograms of drug that potentially can be sold or some others would come -- I personally would like to see --- activity or whatever. But what I am seeing that we are spending a lot of time on Dr. Angulo's preference, and we may be missing focusing on which are the most important one or two questions that we would like to ask in terms of safety and effectiveness.

If we could come up with which is the most important thing that will determine -- in this case, I think safety

because effectiveness is on the side -- but in terms of is this drug potentially able to produce resistance, I haven't come exactly with the answer to that.

But even I came with not a very high enthusiasm for the Framework, I think that just this classification of, you know, things that are very similar to the drugs used in humans and how much the thing is going to be exposed is as good as anything else that I have been listening.

So, except if we come with something better, I am not listening or I am not hearing anything better other than Dr. Angulo's, you know, proposal of five things. I think his opinion are good.

I can come with another five and obviously here we have been seeing some others, three or four or five or whatever. So if we cannot come out with something better, I'm revisiting in my mind the things that I learn in the Framework.

CHAIRMAN MORRISON: If I understood, I would urge you to think about those four or five or whatever they may be, objectives that you would like to see the pre-approval studies conduct or accomplish because if we don't come up with any, then we're going to have what we have here.

DR. SAGRIPANTI: I'm a little concerned because, again, all these suggestions come mainly from people that will never have to do a review, and I am very sympathizing with the people that will have to handle this thing.

So I can only think in my mind of two scenarios. One is in which things go with the Framework are not, you know, very precise and some people, you know, may come up once in a while, saying, oh, my drug took longer than it should, or maybe I was a little unfair putting class one or two and maybe it's not going to be, you know, universal happiness.

But the other scenario that I am envisioning is that we are going to keep thriving for some perfection that will make any of your drugs sit in your desk for ages without end and that perfection will be practically achievable, will be a nightmare for the reviewer, and you are going to just have to sit in potentially good antibiotics. So, pragmatism versus philosophical truth and I will go with the pragmatism at this point.

DR. SUNDBERG: Paul Sundberg, NPPC. It would seem that, based on Scott's comments, that the objective really -- he used the term vector in the post-approval process -- the objective for the pre-approval studies, then, would be to characterize the agent such that you can lead to a characterization of what you need to do post-approval.

And these objectives, these five points, are not as much objectives as they are methods to help do that, so the objective, I would submit that the objective of the pre-approval would be to help direct the intensity of the post-approval monitoring of their post-approval system. And

then, how do you do that? How do you characterize that to get to that point?

MR. SCHUSTER: Dale Schuster, Schering-Plough. Paul, I think you make an excellent idea. My view, and I think that of many people, is that the critical safeguard is going to be their surveillance and monitoring of what happens.

And the best that we can hope for, pre-approval, given all of the limitations and the technology, the best that we can hope pre-approval does is guide the post-approval monitoring in a way that's most effective.

CHAIRMAN MORRISON: So as an objective with the pre-approval studies, if we were to go back one step, it would be to develop the information to guide the post-approval process. Okay.

One of the -- if we've got more -- are there more ideas on these positive aspects, limitations of what we've heard so far with our ability to characterize a drug's development of resistance and ability to impact pathogen load before we move on?

DR. BROWN: Scott Brown, Pharmacia & Upjohn. Throughout the last day and a half, I guess I was struck by the do-ability, if you will, of the in vitro studies as compared to the in vivo studies.

And I go back again, if what you've just said is correct, that we're trying to guide the ultimate thing which is

the post-approval monitoring, then what we have to look at is a battery of study or studies that will be unachievable, that will be interpretable and that can be used, then, to guide that ultimate surveillance of resistance development.

With that in mind, I look at the degree of complexity and the logistical difficulties of the in vivo studies that have been described in the hundreds upon hundreds of questions that have been raised to consider.

And I wonder if, even if we were to be able to standardize the approaches for those things, for the in vivo studies, would we be able to interpret those studies adequately to make decisions about the rational implementation of post-approval monitoring?

If I were to come down on one side or the other, I guess I would come down on the side to say that if the in vitro studies, with their -- the ability to put the appropriate controls in, would be more interpretable and would be more likely to be able to guide the post-approval monitoring whereas the in vivo models and so forth would be remarkably difficult to interpret and to use in that guidance.

CHAIRMAN MORRISON: Because there are so many variables that can impact on the outcome? And so, you would urge standardization of the in vivo study designs?

DR. BROWN: Scott Brown. I guess I would urge the standardization of any studies that we're doing, whether

they're in vitro or in vivo. My concern is that even if we standardize the in vivo studies, we may not be able to interpret them and to provide a relevance to what the real world situation would be.

DR. McEWEN: Scott McEwen, University of Guelph. I think I understand where Scott's coming from but I don't -- I can't really believe him literally because that sort of throws out the entire basis of experiments in science, and I know he didn't sort of mean that.

It probably means that there is a lot of -- a large number of variables and we probably can't expect to set up a set of experiments or observational studies or modeling studies to be able to address all of them.

And I guess my recommendation would be to make an effort to prioritize them and focus on those questions. As Paula Cray would say, try to answer one question with one study and there needs to be a concerted effort to identify a very short list of questions that need to be answered, and then we'll just have to let the rest go, I guess.

So, prioritizing the questions to be answered, narrowing the list down considerably and then designing the combination of in vitro/in vivo studies, I guess, that could reasonably answer those questions.

And just while I'm here, I'd like to make a pitch for trying to make sure that any studies that are done address the

various levels of organization that pertain to these issues. That's the organism, the animal and the population.

DR. BYWATER: Robin Bywater, Pfizer. If I could back up what Scott was saying about -- the Scott -- Pharmacia/Upjohn Scott, but I do believe that we have -- and we've heard only too clearly yesterday, so many questions regarding how in vivo studies could be carried out are the number of variables.

The questions are -- well, they were just going on and on. And what I think I would claim, and I think he was saying, is that, whatever in vivo study that you use in a pre-regulatory process, it will probably give you little extra to build on.

Out of them you could get from the in vitro studies that I think we agree are more practicable and doable. So, the idea that you have to do in vivo studies because the live animal is what matters is really a bit misleading. The animal that matters and the population that matters is the one that's going to be exposed to the drug after the approval process, out in the field.

And I would back up the need for post-approval monitoring to be specific, thorough and organized in a way that will intrinsically give the protection that we're looking for to the population as a whole.

CHAIRMAN MORRISON: So if I'm understanding, let me just -- Robin, your point, and I think Scott's point and maybe

Scott's point before that, is referring to, actually, our second question which is, how do you value and how do you use the various kinds of information that we're going to gather in pre-approval studies? And so, if I understood correctly, it was you would look to the post-approval process for most of your in vivo data collection.

DR. BYWATER: And I think the idea that was I think referred to in passing, that you would do a field study in a pre-approval process. It seems to me an impracticable thing to do because, again, you're dealing with a situation which is a new drug and a new environment before the things have settled down and you'll get some probably misleading results as a result.

CO-CHAIRPERSON SINDELAR: Can I ask, when you're looking at this as a pre-approval -- let's say, for example, this is information gathering and you're looking at this for post-marketing approval, are you looking at this possibly as a conditional approval with post-marketing surveillance that ultimately supports approval as a, perhaps a --- like a possibility?

DR. BYWATER: Robin Bywater, Pfizer again. Well I think if you're going to have post-marketing surveillance, implicit in that is that there has to be an assessment of what those surveillance figures are going to show and they may well show that something needs to be done.

Now, that thing that needs to be done doesn't necessarily mean the product has to be taken off the market, but it may mean that the way in which isn't being used needs to be reviewed or the label indications or extra precautions placed on it.

So, post-marketing surveillance does imply a reaction at a certain -- and this dreadful word comes in again, threshold. But what we've certainly got to be aware of is setting arbitrary and demanding thresholds, the one percent that has been bandied around in the past, fills everyone with horror and it really doesn't make any sense. But, nevertheless, surveillance implies reaction at some stage.

CO-CHAIRPERSON SINDELAR: Yes. And you're getting to this threshold. I mean, I'm looking at, at what point in this process of determining the risk benefit analysis of its use, and would it be able to be part of the process whereby you may actually remove a drug, you know.

It may, ultimately, support a wider labeled use of the drug. I mean, you're looking at both ends of a positive or a negative. But to accept, you know, as part of the -- I'm trying to understand where the decision points are as a result of this information gathering.

DR. BYWATER: You're talking about now the pre-approval process?

CO-CHAIRPERSON SINDELAR: If you were to look at

these as information gathering, and they're going to take it out to on-site farm use and expand its use, are you looking at a conditional approval or are you looking at an approval with contingencies that, you know, looking at Framework, you know, which would apply to antimicrobials that are already approved, some kind of framework that would take them off of the market and that is looking at thresholds.

DR. BYWATER: Well, I think you're covering two things there. When you go back and talk about the products that are approved because I think that, in a sense, is a different kettle of fish because you're then dealing with a situation which you can assess as of now as opposed to the future.

But if you're talking about a new compound that has gone through the pre-approval process, has been put on the market and then is subject to post-marketing surveillance, one has to accept and assume that built into that surveillance process will be some review with potential action.

CO-CHAIRPERSON SINDELAR: New action? New potential action?

DR. BYWATER: Yes. And what those actions are and how that review is carried out is a matter for another day's discussion, I suspect.

DR. VAUGHN: Michael Vaughn with Bayer Animal Health.

As a point of clarification for the group, currently the Agency does not require post-approval monitoring. Okay? It's my understanding that it was an agreement between Bayer and CVM that as poultry was approved and as cattle was approved that we would do a voluntary post-approval monitoring it and we did it for three years on poultry and we've done it for one year in cattle.

But as the comments to the Framework document were published in December, the Agency has decided that post-approval monitoring will no longer be required as a part of the continual drug experience report, yearly. And so, any post-approval monitoring today is on a voluntary basis.

DR. FLYNN: I think the pre-approval studies, I think we're looking at this as one piece and a system a various pieces that may be working to try to address the issue of resistance, one of which is a post-approval monitoring of some type and I think a lot of people have said that, you know, that's where the rubber really hits the road with this thing, is post-approval monitoring.

Now, whether it's done through various product specific actual monitoring programs or whether it's through the national system, but right now, basically the emphasis seems to be moving towards strengthening the NARMS system as the mechanism by which post-approval monitoring occurs.

So, in the context of that, I mean, there may not be

specific monitoring for each product. In an environment where we have a national program of monitoring resistance, the question then becomes, with regard to the pre-approval studies, you know, what role can that play in the overall objective which is the public health impact of resistance.

So, when looking at the -- going back to the main objective of the study, is back to the guidance which refers to evaluating or characterizing the rate of resistance development, it may be that, you know -- so how can pre-approval studies help to try to address that safety question?

It may be that we decide that by looking at the way the science is today that it would be nice if it could predict what's going to happen in the future but maybe that's unrealistic. Maybe the science is just not there that we can predict it, but what else can pre-approval studies do to help address the issue of the rate and extent of resistance development?

I mean, how can those studies be used as a piece in the overall plan of trying to control the -- or to address the safety question. So I don't think we have to be limited to saying that it just has to be a predictor. I mean, perhaps the answer is, no, it can't predict but -- so if that's the case, what else can it do?

You know, can it help us to optimize how the drug is

-- what kind of dosing regime, dosage forms, other -- can it help to optimize the way the drug is used so it can minimize resistance in the end.

CHAIRMAN MORRISON: So Bill was challenging us to think about the role of pre-approval studies, really in the post-approval process, which we sort of heard, is probably going to be there.

So if we can't -- we said earlier we can't -- we don't think we can predict, was what I heard, in our series of in vitro and in vivo experimental studies in the pre-approval process. We don't think we're going to be able to really predict the development of resistance in the field. Did I hear that right? And so, we will therefore have some post-approval process. Scott.

DR. McEWEN: Scott McEwen, University of Guelph. I'd be a little uncomfortable saying we couldn't predict anything based on the pre-approval studies. I think it would be fair to say that we wouldn't be able to be certain what's going to happen in the field based on pre-approval studies.

But it should be possible to devise some studies which would give one an idea of some of the important factors that could happen in the field. For example, if a drug had a propensity for developing resistance easily, then presumably a screening type study, either in vitro or in vivo, would sort of pick that up where conversely, if there was very little for

propensity for resistance development, that should be identifiable in a screening set of studies.

But how that's exactly going to translate in terms of prevalence to resistance in the field -- so I think it's a question of will we be able to predict with accuracy and precision? No. Will we be able to get an idea of what could happen? Probably. And I don't think these studies could rule out anything but they could certainly give an idea of what's going to happen.

You know, we came up with that list of the categories of studies and I guess the question is where the positive and the limitations of each. Could I just maybe run through some personal thoughts on those?

We had the in vitro studies on individual organisms, I guess, and also the one type of in vitro study involving -- attempting to mimic the gut ecology. It seems to me, in general, the advantages of those studies are that you could do a lot of screening.

You could attempt to address a large number of the issues that were raised or the questions that would be -- we would want to answer, look at a lot of bug/drug combinations in a variety of scenarios and there's sort of lots of flexibility and -- so in terms of screening tests, that there's a lot of advantages to those.

I guess in terms of the limitations, in general we

don't know how events that happen in vitro apply to the real world situation, as with any experiments, so that's a limitation.

Anything that depends on the sort of complex interaction of the large number of organisms that exist in the gut or in the environment or anything that -- we wouldn't be able to address all that kind of host and environment -- some of the host and environment factors in the vitro system.

I guess the other kinds of studies that we heard about were the kind of classical animal experiments. We assembled groups of calves, for example, and inoculate them with sensitive strain and donor organisms and see if there's uptake under -- uptake of resistance under antibiotic pressure, that sort of thing.

I guess the advantages there that we can have some degree of control over the variables of interest. We can evaluate those kind of nebulous host related factors that are part of the advantage of doing things in vivo, or complex, I guess, of the organisms of the gut, all the things that the in vivo environment.

The disadvantages, many have outlined those. We can only -- because of the constraints we have on animal numbers and facilities and finances, we could only reasonably do a limited number of those so we can only address a few questions and a few sort of organisms, presumably, and we'd have to focus

in on the questions we want to address.

The next kind of category, I guess, was the sort of real world, on farm type of studies, the observational studies or clinical trials if you want to call them that. The advantages are that that's real world exposure, in a sense of organisms, both zoonotic enteropathogens and commensals and resistance determinants that may be out there in nature, I guess.

And so, it is sort of is that much closer to the real world. The disadvantages are that we presumably have a larger number of uncontrolled variables that we can't measure. We have -- you know, epidemiologists have ways of attempting to deal with those but it's imperfect, in a sense, and so we run the risk of having uncontrolled compounding and so on bias our results.

Other disadvantages of those is a tremendous cost, the difficulty of doing them that go without saying almost. The modeling study has already touched on, I think, my perspective on the advantages and disadvantages of those.

CHAIRMAN MORRISON: Anything anybody wants to add to Scott's advantages/disadvantages of mathematical modeling, in vitro testing, in vivo experimentation and in field trials? Steven.

MR. FONDRIEST: Steven Fondriest, Union of Concerned Scientists. And perhaps it's more of wording, but with one of

the limitations that said limited predictability of what would actually occur in the field and that sort of begs the question -- it's number three -- what's the purpose of doing pre-approval studies if they have no predictable use for post-approval situations?

So, maybe it's just another wording is needed, but I think that the pre-approval studies do have -- should have some benefits in terms of predicting what would actually occur in the field and perhaps that would suggest that just doing the -- there are some cases where in vitro studies are more appropriate than in vivo studies in the pre-approval development, and such things as actually looking at interactions between the antibiotics and the intestine of the animal and other animals in a farm setting could provide more predictive information than what you would find strictly within a laboratory setting, or towards the interactions between other pathogens or other bacteria within the flora of an animal.

It could also -- you could provide -- develop some very interesting information that would not necessarily be available if you only did in vivo studies. So I think those should be considered, that perhaps could address the issue of limited predictability that you actually could find in the field.

MR. ANDRES: Chuck Andres, CVM. I think when I wrote that down, people were discussing the overall applicability of

pre-approval studies. I think someone had said that when the rubber meets the road, that's when it's approved.

When you really start -- get your information as to what's going to happen in a real world, and that all the pre-approval studies in the world are not going to give you as good of an answer as throwing it out there, effectively monitoring it and then what's happening in the real world under use conditions. And if we need to reword that or we need to add another one, we can do that.

MR. FONDRIEST: Perhaps just suggest that we would prefer to have the most robust pre-approval system that was possible, and if in vitro is the way to do it, that might cost more. It might take more time to do, to develop those and to get good answers, but then that's what's necessary before registration -- before approval could be given to an antibiotic.

(Long pause.)

CHAIRMAN MORRISON: We're just trying to incorporate Steven's comment in here and we're struggling with how to do that.

(Laughter.)

CHAIRMAN MORRISON: Well, let me just -- is there agreement from what I said previously in that there was an initial -- someone, I don't know who it was, is someone concerned that there is limited predictability of these -- of

ultimate resistance, post-approvably (sic), in pre-approval studies?

DR. BYWATER: Robin Bywater, Pfizer. I would support the wording as it stands because I think that's exactly the case.

CHAIRMAN MORRISON: Okay.

DR. BYWATER: There is a limited predictability and that's a fact.

CHAIRMAN MORRISON: Okay.

DR. BYWATER: So it's not that there's no predictability, which is what I think Steven was implying. It's limited, and I don't think we -- well, I don't think it needs changing.

MR. ANDRES: And what my suggestion is, we can add an additional -- I mean, again, we're trying to assemble what were the issues that were raised in this session so when we go back to the general session, they can be presented and then we can all go behind closed doors after this over with and figure out where we go from here. So I don't want to stifle anybody. If you don't feel like your thought has been accurately scribed -- I was looking for the right verb --

MR. FONDRIEST: Agreeing that limited predictability of what would actually -- there is limited predictability and a solution to that would be to develop very robust pre-approval programs which would include in vitro, if necessary, over in

vivo.

DR. BYWATER: I think you mean the other way, in vivo over in vitro.

MR. FONDRIEST: Yeah, sorry. Sorry about that. And that could get around this issue of -- I mean, what we want is to develop a strategy which will provide the best information possible and that might require spending more money, spending more time to get good information and that will help alleviate some of this -- the limited predictability of what actually will occur in real settings.

MS. PATTERSON: Deborah Patterson, Biotechnical Service, Inc. I kind of come from a different perspective. I'm, by training, a geneticist, so I have a lot of modeling and statistics.

You're not going to be able, in any pre-approval setting, perfectly predict or model or even probably come close to what you're going to see in the field. What you can do with your studies is set your targets, I guess.

And in that sense, I guess I would tell you that I would support a pre-approval system based on in vitro work and then following up with post-monitoring, and that's where you can really use your mathematical modeling because here you are gathering all your data, all your variables, and what you're able to do is use your mathematical models there to predict as actual use because that's the other thing -- we're assuming

everybody's going to use the drug correctly. We're not actually -- I know; don't start making faces at me, Chuck.

MR. ANDRES: I'm not. I'm just --

MS. PATTERSON: What you're trying to say is, what's going to happen out there in the field? What kind of exposure? What kind of risk are you putting yourself at? And I think you can't answer that, pre-approval.

There's no study you can set up. There's nothing you can do that will predict that, ultimately. But I would say to you that you can certainly develop strategies to do it post-trial -- post-approval.

CHAIRMAN MORRISON: I think we have in -- so Chuck, I think we have that in an objective earlier. One of the objectives of the pre-approval studies is to provide information and target information for the post-approval monitoring and surveillance.

MR. ANDRES: Yes, determine level of vigilance necessary, post-approvaly (sic.)

CHAIRMAN MORRISON: So Deborah, I think we incorporated that thought at an earlier objective. Okay.

DR. SILLEY: Peter Silley, Don Whitley Scientific. I just concur with the last speaker, but I just really wanted to return to that limited predictability. I think we have the privilege of working with a number of different sponsors and I think everybody would love to have models with a high level of

predictability.

And I think that what our limitation is, is basically our knowledge as the science --- and the reality is that those models which have been worked on are not able to give us that. And I think it's important that we realize that it's not that anybody -- I think everybody in this room would want to have a high level of predictability, if indeed it was possible.

But I think we need to be realistic and with the tools that we've actually got available to us at the moment when we can't do any better than that limited predictability.

CHAIRMAN MORRISON: Let me throw this out -- I would suggest one word that's different and that would be unknown predictability, basically because you may have an in vitro or in vivo test that may be incredibly predictive, but we never know if it's going to be predictive or not. So that denotes or to me suggests that they're always limited and that may not be the case. They may be wonderful.

DR. SAGRIPANTI: Sagripanti from Devices, again. What I am listening to the big problem on this pre-approval studies is the lack of predictability and I have two comments on that.

First, it seems that everybody's drifting to, okay, let's not --- so many in the pre-approval and let the post-market surveillance do their job, but I hope that everybody in the industry remember that there's only one thing

more expensive than not having your drug approved, is that having your drug approved and have to retrieve it from the market.

So I think the value of pre-market approval is very important. I just thought, and maybe it's not right or whatever, but I think that the big limitation is that we are trying to make this absolute predictability and with so many thousands of questions, that may be as well impossible.

What if we just make some relative prediction. Compare, let's say, to campylobacter and fluoroquinolones, and we assign to that like a golden control or something. If anything else, give less mutants or less resistance or whatever, we assume that it's less and safe, that same standard. If nothing gives five times more, it's obviously a problem, but maybe going -- you know, I am not sure if I would support that forever but that just came to my mind.

Instead of going to this absolute estimation which so far has proven to be futile -- we have been here for a couple hours and we haven't got there. Think somehow in a different perspective.

What about a relative -- you know, substantially equivalent to the resistance produced for something which is out there, Vancomycin, whatever. But maybe that may let us get out of this trap in which I feel we have been for a while.

MR. FONDRIEST: Steven Fondriest, Union of Concerned

Scientists. This is just perhaps a clarification but -- and please tell me if I'm wrong. I thought that the Framework says that the post-approval studies are more for monitoring, or when we reach that resistance threshold, so that either a product could be withdrawn or the use regime could be changed.

And so, perhaps that states that -- I mean, if that's the approach, which is what I'm taking, from how I interpreted the Framework, the purpose of the post and the pre-approval studies are different than if -- or just different.

MR. ANDRES: (Inaudible comment/away from microphone.)

CHAIRMAN MORRISON: Chuck's comment is that he didn't want to, in this session, discuss the Framework document because it's open for discussion and anything you want to put in there, you can make a suggestion. So, is there any follow up on the comment that we have a relative standard or "gold standard" and that become relative standard and that that become something that we compare it to --

DR. BYWATER: Robin Bywater, Pfizer. It's an attractive idea that you can set a standard and then judge everything else against it. I have considerable concerns that this would not actually be at all a straightforward process because of the -- all organisms are not the same in terms of their risk to human health.

The way in which antibiotics develop resistance is

not transferable -- not equatable from one to another. The whole thing is so variable that I think each one has to be thought of on its merits. So, attractive as the idea is, I would be worried that whether it could ever work.

CHAIRMAN MORRISON: I suppose what it is, is it's an idea for that threshold, isn't it? It gets back to that because you're going to need something, if there is a threshold in place, to say yea, nay, and that's really a suggestion for it.

MR. ANDRES: Down here, we get it approved; up here, it does not happen.

DR. BYWATER: It's not precise.]

DR. SAGRIPANTI: As you start developing more and more antibiotics, then you start having closer and closer standards.

CO-CHAIRPERSON SINDELAR: Please use the microphone.

DR. BROWN: Scott Brown, Pharmacia & Upjohn. I think the idea of having the gold standard or the threshold makes some sense in one respect and that is that, regardless of, Robin, in the case -- you can't use one size to fit everything. That's absolutely true.

But the last thing I think a pharmaceutical company wants is to be able -- is only to know whether we pass or fail at the eleventh hour. We'd rather know up front what the criteria are and so perhaps for our particular situation for

whatever study we have to do, we design some decision criteria.

We conference with the Agency which is the -- one of the standard processes that CVM has, and we have the opportunity to understand, up front, at the beginning of the process, what a criteria are for a successful passage of the study or not, and that way, you're right.

I mean, the worst thing is that you spend all the money and you get the product approved, or you spend all the money and you don't get it approved at the eleventh hour.

We'd rather know up front what those things are and I think if we can maybe come to some -- maybe have a bullet point up here in general comments that maybe there's no one size fits all standard, but that the standard for each particular situation would be decided a priori for the sponsor but in the negotiations between the sponsor and the Agency. That might be a little more palatable, at least one thing that just comes to mind as we're talking here.

CHAIRMAN MORRISON: And I'm hearing you, Scott, reiterate perhaps something that Steven said, that try and have these pre-approval studies as robust as possible to screen out products that don't look like they're going to make it later.

DR. BROWN: Yeah, I think in concept you'd like to have something as robust as possible. I think we also need to recognize that -- what the limitations are in that robustness and make sure that we don't over-interpret studies that may not

be as robust as we perhaps would like them to be.

DR. BYWATER: Robin Bywater, Pfizer. If I could just take up the one word that Scott used just then, over-interpreting. I think we should, in all of this, have at the back of our minds an awareness that although antibiotic resistance is a major issue and although we're developing and registering drugs, antibiotics for use in animals have responsibility towards it, we shouldn't get it out of proportion.

Most antibiotic resistance in human patients has nothing to do with animals at all. It's a very small minority but it's a minority that we should be concerned about. But equally, to build a great edifice of which every compound has to struggle, and most of which will drop off in the process because we're concerned about this to an unreasonable degree, I think is something we should be wary of and we should try and keep a sense of proportion about the whole process.

CO-CHAIRPERSON SINDELAR: Unfortunately, we have to be out of this room in ten minutes, so what I'm going to ask is that we just have a brief overview of what we've come to agree as far as part of our presentation and response to what are the objectives of the pre-approval studies and response to number -- questions number one and two. And we can leave this for tomorrow to make any, you know, final comments.

CHAIRMAN MORRISON: Okay, Chuck, let's look at our

first one. Is this our first slide?

MR. ANDRES: It's our first slide.

CHAIRMAN MORRISON: All right. We spent quite a bit of time trying to figure out, are these studies merely a body of knowledge or is each one pivotal, and we found out later that, yeah, each one is quite pivotal, quite important and all of that is extra stuff.

MR. ANDRES: Superfluous now.

CHAIRMAN MORRISON: Yep. Okay. Let's go to our next one. So we said then, all right, what are the objectives given that, and we said, well, obviously, one is to characterize the rate and extent of resistance development which is already in there.

And oh, another one that we said, well given that, it sounds like there's going to be post-approval monitoring/surveillance/review. These studies may as well generate some information that will be helpful in that process.

Let's see. Oh, yeah. We were -- maybe that should go into our general comments but we're concerned, overall, about how these studies and the outcome of these studies are going to be used in the decision making process. Okay.

We thought that an objective of these studies could be to change or influence the category or the category/use that a drug is placed into. Given that you're going to learn some information in these studies, if that was possible, we'd like

to see that. And I think it's redundant because you've got the H, M or L up above. Okay.

Then we said, all right, what do we think about these points and we thought that other than number four, we thought that, at least one, two, three and five were accomplishable and that they would give valuable information towards the other objectives, the overall objectives of information for resistance development.

Then, let's see now. Then we said, all right, what study concepts were reviewed and this was just to remind ourselves and we said, well, we had some mathematical modeling, some in vitro, some in vivo and I don't recall anybody presenting on-farm studies, but that would be, obviously, another -- field studies, that would be another data source.

And we said, what are the advantages? What did you like about what you heard? What were the limitations of what you heard? Paul?

DR. SUNDBERG: Just as a point of clarification, and Paul Sundberg, NPPC, or National Monogastric Producers Association.

(Laughter.)

DR. SUNDBERG: Yeah, National Monogastric Producers. Go back -- yeah, on-farm studies. If you're talking about field studies, they'd much rather have you be specific and say field studies than on-farm studies.

CHAIRMAN MORRISON: Okay. And so, this was just a reminder of what those studies were, the data sources. All right. So what did we like, or what did we think? We said that the existing method, and if I remember correctly, that is for measuring pathogen load, is not adequate, but pathogen loads probably have -- pathogen load studies have some value; for example, in the food safety arena.

Math models enable us to test hypothetical scenarios. Possible effects of intervention could fit into risk assessment. I'll speak for mathematical models -- force you to ask the questions that you need to ask. In vitro studies -- I don't remember that one. Did we say that?

MR. ANDRES: You said that.

CHAIRMAN MORRISON: In vitro studies are more interpretable for post-approval use than in vivo.

MR. ANDRES: Pre-approval studies done in vitro versus in vivo pre-approval.

CHAIRMAN MORRISON: How about are more repeatable? I don't know.

MR. ANDRES: Trying to remember back.

VOICE: Predictive.

CHAIRMAN MORRISON: More predictive, are we saying? More repeatable?

DR. REDMAN: Interpretable --- saying so many variables --

MR. ANDRES: Right. You can interpret the in vitro study better because of the limited number of variables in there as opposed to an in vivo study. Whether it is predictable is a whole other issue. This is what's a positive aspect of the study concept?

Well, in vitro studies are nice because they're nice clean, controlled where you can interpret what the results mean. However, for post-approval use -- now I'm not sure why that got in there and that's where I guess we're confusing people.

CHAIRMAN MORRISON: Was this -- I don't know whether this -- well, there's too many Scotts. I'm not sure which Scott --

(Laughter.)

DR. McEWEN: He was talking about intrepretibility. I went through some --

MR. ANDRES: You went through a list of things and I tried to keep up with you

(Laughter.)

MR. ANDRES: And if this is from you and this isn't right, tell me what it was you -- and I'll change it.

DR. McEWEN: I don't remember saying anything about interpretibility. I guess what I -- my thoughts were, that in vitro studies, the advantages were that you could screen a larger number of variables, organisms and drugs and issues.

Because of the cost limitations, the fact that you've got tighter control over it and the technical issues allow you to, I would think, answer -- address more questions.

The limitations are that it's that much further removed from the real world that we don't have the other variables -- are you typing, getting all?

MR. ANDRES: Yeah, I took speed typing.

(Laughter.)

DR. McEWEN: That because we're only usually looking at -- in a very controlled situation, then it doesn't tell us as much about what's going to happen in the field. That would be my guess there, sort of hierarchy of --

MR. SCHUSTER: Well really, the advantages of in vitro really it's disadvantages when you talk about going in the field.

DR. McEWEN: Yeah, they're complimentary as you go down, you could make up a list of the advantages of in vitro and in vivo in animals and then in the field situation and the modeling would sort of mirror the disadvantages of -- if we put those in reverse order, they would --

CHAIRMAN MORRISON: All right. And then we were saying, well, what are the limitations of some of those experiential models not in field testing where that -- we had limited number of host/environment factors that we could study.

MR. ANDRES: Let me go back one more.

CHAIRMAN MORRISON: Okay.

MR. ANDRES: Let's start there; that's where we were with limitations.

CHAIRMAN MORRISON: Oh, okay. Limitations of the studies that we heard this morning, mathematical modeling, in vitro testing and in vivo experimental models, where that -- let's see -- pathogen load studies should be eliminated. Okay. So it's --

CO-CHAIRPERSON SINDELAR: That was a statement.

MR. ANDRES: That was more of a statement.

CHAIRMAN MORRISON: That was a statement?

CO-CHAIRPERSON SINDELAR: That was a statement.

CHAIRMAN MORRISON: Okay. Mathematical models, the expertise available is limited, require the assumptions that are open to challenge -- yeah, full of assumptions. Limited predictability of what would actually occur across all of these experimental methods and we want to develop robust pre-approval studies if and when necessary.

MR. ANDRES: Well, I think that this one is, and we can fine tune this later, but the purpose of this one was --

CHAIRMAN MORRISON: The purpose of this one was to address your concern. I think it's another Steven. Is that even though expense may be an issue with the in vivo, it may be necessary to go that route to get a better answer, predictive answer. Is that --

MR. WHITE: Are we only listing the limitations of the mathematical models?

CHAIRMAN MORRISON: No, in general.

MR. ANDRES: Yeah, next page we talk in vitro, in vivo ---

MR. WHITE: Okay. Can we go back to that previous one? I just wondered why that limitation on the models is there on its own. I mean, all these approaches have limitations and advantages.

MR. ANDRES: Let me explain my shorthand. The specific example, if there was a specific example given per the type of testing, I started the point off with that type of test. If there was no specific test given, if it was a general about all pre-approval studies, then it's got no preface.

So when I say limited predictability of what would actually occur in the field, again, we discussed that earlier, that is all pre-approval studies were going to be limited to what we're going to be able to predict when we turn this thing lose, post-approvaly.

And then, to accommodate a second viewpoint, we put in develop more robust pre-approval studies. That's across all study types and maybe choosing in vivo, a more resource intensive exercise over in vitro if necessary.

CHAIRMAN MORRISON: You're done.

MR. ANDRES: I'm done.

(Laughter.)

CO-CHAIRPERSON SINDELAR: Hi. We'll leave on this note. We are really being asked to remove ourselves from this room.

DR. BROWN: Can I make a quick request, and that is to have those printed out and available by first thing tomorrow morning, like at breakfast time, so that we can take a look and we can make some comments and be ready at 8:30, to have comments?

CO-CHAIRPERSON SINDELAR: Your request is well received; yes.

DR. BROWN: Thank you.

CO-CHAIRPERSON SINDELAR: Thank you.

SAGRIPANTI: I assume that the standards didn't make it to the list, right?

MR. ANDRES: No, no, no; it's there.

CHAIRMAN MORRISON: It's there. We'll get these to you tomorrow and we'll start from here tomorrow.

CO-CHAIRPERSON SINDELAR: Right. Thank you. Reminder, the reception will be right here at 5:30.

(Meeting adjourned, to reconvene Thursday, February 24, 2000 at 8:30 a.m. in the gazebo area.)